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MOST NEGATIVELY CHARGED SUBFRACTION (L5) OF PLASMA LDL PROLONGS ACTION POTENTIAL DURATION OF RAT CARDIOMYOCYTES VIA LOX-1 RECEPTORS

ACC Poster Contributions
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Background: Dyslipidemia has been associated with increased incidence of ventricular arrhythmias during myocardial ischemia. L5, the most negatively charged subfraction of circulating LDL identified in patients with hypercholesterolemia and diabetes, was shown to induce vascular endothelial cell apoptosis that requires L5 internalization medicated by the lectin-like oxidized LDL receptor (LOX-1). However, little is known of the effects of L5 on the electrophysiological properties of cardiomyocytes (CMs).

Methods: L1-L5 subfractionations of hypercholesterolemic human LDL (>130 mg/dL), according to their electronegativity from the least to the most negatively charged, was extracted by ion-exchange chromatography. Embryo rat CMs (H9C2) were exposed to two concentrations of L5 and L1 for 15 minutes and 24 hours, respectively. Whole-cell patch clamp technique was used to record action potential duration (APD) and membrane currents.

Results: Internalization of labeled L5 was observed in CMs by fluorescence microscopy. Clinically relevant hyperlipidemic range of L5 (7.5μg/mL) acutely prolonged the APD of CMs (<3 minutes) (235.7±30.9ms, vs. baseline 148.1±20.3ms, $p<0.01$ n=5) whereas L5 at 2.5μg/mL did not (184.3±54ms, vs. baseline 141.7±13.5ms, $p=0.24$, n=4). L1 did not prolong APD even at a high concentration. Pretreatment of CMs with TS20, a LOX-1 neutralizing antibody, prevented L5 internalization and L5-mediated APD prolongation (159.5±46.0ms, vs. baseline 168.1±44.3ms, $p=0.33$, n=5). After 24-hour incubation with L5, APDs were significantly prolonged at both concentrations (245.6±14.1ms at 7.5μg/mL, and 249.9±27.0ms at 2.5μg/mL, $p<0.01$) compared to placebo (150.6±8.9ms). Incubation with L1 did not effect on APD (181.4±18.0ms in 7.5μg/mL, $p=0.14$ and 169.6±31.2ms in 2.5μg/mL, $p=0.44$, vs. placebo). The outward repolarization membrane currents, elicited by a ramp protocol from 60mV to -100mV, were significantly reduced by L5 perfusion of 7.5μg/mL ($p<0.01$, n=4).

Conclusion: Our findings indicate that L5, when internalized via LOX-1, prolonged APDs of CMs by reducing outward currents, which might contribute to arrhythmias in patients with hypercholesterolemia and/or diabetes.